

The Critical Role of Mast Cells in Allergy and Inflammation

THEOHARIS C. THEOHARIDES,^{a,b,c}
AND DIMITRIOS KALOGEROMITROS^d

^a*Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Tufts–New England Medical Center, Boston, Massachusetts 02111, USA*

^b*Department of Biochemistry, Tufts University School of Medicine, Tufts–New England Medical Center, Boston, Massachusetts 02111, USA*

^c*Department of Internal Medicine, Tufts University School of Medicine, Tufts–New England Medical Center, Boston, Massachusetts 02111, USA*

^d*Allergy Division, Attikon Hospital, Athens University Medical School, Athens, Greece*

ABSTRACT: Mast cells are well known for their involvement in allergic and anaphylactic reactions, but recent findings implicate them in a variety of inflammatory diseases affecting different organs, including the heart, joints, lungs, and skin. In these cases, mast cells appear to be activated by triggers other than aggregation of their IgE receptors (FcεRI), such as anaphylatoxins, immunoglobulin-free light chains, superantigens, neuropeptides, and cytokines leading to selective release of mediators without degranulation. These findings could explain inflammatory diseases, such as asthma, atopic dermatitis, coronary inflammation, and inflammatory arthritis, all of which worsen by stress. It is proposed that the pathogenesis of these diseases involve mast cell activation by local release of corticotropin-releasing hormone (CRH) or related peptides. Combination of CRH receptor antagonists and mast cell inhibitors may present novel therapeutic interventions.

KEYWORDS: asthma; coronary artery disease; inflammation; dermatoses; mast cells; skin; stress; vascular permeability

SELECTIVE RELEASE OF MAST CELL MEDIATORS

Mast cells are necessary for the development of allergic reactions, through cross-linking of their surface receptors for IgE (FcεRI),^{1,2} leading to degranulation and the release of vasoactive, proinflammatory, and nociceptive

Address for correspondence: T.C. Theoharides, Ph.D., M.D., Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA. Voice: 617-636-6866; fax: 617-636-2456.

e-mail: theoharis.theoharides@tufts.edu

Ann. N.Y. Acad. Sci. 1088: 78–99 (2006). © 2006 New York Academy of Sciences.
doi: 10.1196/annals.1366.025

mediators that include histamine, IL-6, IL-8, PGD₂, tryptase, and vascular endothelial growth factor (VEGF).³⁻⁵ Mast cells derive from a distinct precursor in the bone marrow^{6,7} and mature under local tissue microenvironmental factors.⁵ In addition to stem cell factor (SCF), mast cell chemoattractants include nerve growth factor (NGF),⁸ RANTES, and monocyte chemoattractor protein 1 (MCP-1).⁹ They can secrete a multitude of biologically potent mediators (TABLE 1), giving rise to speculations about their possible role in innate or acquired immunity.^{5,10,11} In addition to allergic triggers, mast cells can be activated by anaphylatoxins, antibody light chains, bacterial and viral antigens, cytokines, and neuropeptides.¹² Immunoglobulin-free light chains appear to elicit immediate hypersensitivity-like responses^{13,14} through mast cell activation and subsequent induction of T-cell-mediated immune responses¹⁵ (TABLE 2). Increasing evidence also indicates that mast cells are critical for the development of inflammatory diseases, especially in the pathogenesis of diseases such as arthritis, asthma, chronic dermatitis, and coronary artery disease (CAD) (TABLE 3).¹² However, unlike the case in allergic reactions, mast cells are rarely seen to degranulate during autoimmune¹⁶ or inflammatory processes.¹⁷ The only way to explain mast cell involvement in nonallergic processes would be through “differential” or “selective” secretion of mediators¹⁸ without degranulation.¹⁹ In fact, this may be the only way this ubiquitous and versatile cell may regulate immune responses without causing anaphylactic shock.

Instead, mast cells can undergo ultrastructural alterations of their electron-dense granular core, indicative of secretion, but without degranulation, a process that has been termed “activation,”²⁰⁻²² “intragranular activation,”²³ or “piecemeal” degranulation.²⁴ During such processes, mast cells can release many mediators *selectively* (TABLE 4)²⁵⁻²⁷ as shown for serotonin¹⁸ and eicosanoids.²⁸⁻³⁰ Triggers include innate molecules, such as stem cell factor (SCF), which releases IL-6.³¹⁻³⁴ IL-1 can also stimulate human mast cells to release IL-6 selectively through 40–80-nm vesicles unrelated to the secretory granules (800–1000 nm).³⁵ Corticotropin-releasing hormone (CRH) can stimulate selective release of VEGF without degranulation.³⁶

SKIN INFLAMMATION

Mast cells are well known for their role in skin hypersensitivity reactions.³⁷⁻⁴¹ Skin mast cells are located close to sensory nerve endings⁴² and can be triggered by neuropeptides,⁴³⁻⁴⁶ such as neurotensin (NT),⁴⁷ nerve growth factor (NGF),⁴⁸ substance P (SP),⁴⁹ and pituitary adenylate cyclase activating polypeptide (PACAP), all of which can be released from dermal neurons.⁵⁰ In fact, skin mast cells contain SP,⁵¹ while cultured mouse and human mast cells were shown to contain and secrete NGF.⁵²

Skin appears to have its own equivalent of the hypothalamic–pituitary–adrenal (HPA) axis,^{53,54} the main regulator of which, CRH and its receptors,

TABLE 1. Mast cell mediators

Mediators	Main pathophysiologic effects
<i>Prestored</i>	
Biogenic amines	
Histamine	Vasodilation, angiogenesis, mitogenesis, pain
5-Hydroxytryptamine (5-HT, serotonin)	Vasoconstriction, pain
Chemokines	
IL-8, MCP-1, MCP-3, MCP-4, RANTES	Chemoattraction and tissue infiltration of leukocytes
Enzymes	
Arylsulfatases	Lipid/proteoglycan hydrolysis
Carboxypeptidase A	Peptide processing
Chymase	Tissue damage, pain, angiotensin II synthesis
Kinogenases	Synthesis of vasodilatory kinins, pain
Phospholipases	Arachidonic acid generation
Tryptase	Tissue damage, activation of PAR, inflammation, pain
Peptides	
Corticotropin-releasing hormone (CRH)	Inflammation, vasodilation
Endorphins	Analgesia
Endothelin	Sepsis
Kinins (bradykinin)	Inflammation, pain, vasodilation
Somatostatin (SRIF)	Anti-inflammatory action
Substance P (SP)	Inflammation, pain
Vasoactive intestinal peptide (VIP)	Vasodilation
Urocortin	Inflammation, vasodilation
Vascular endothelial growth factor (VEGF)	Neovascularization, vasodilation
Proteoglycans	
Chondroitin sulfate	Cartilage synthesis, anti-inflammatory action
Heparin	Angiogenesis, nerve growth factor stabilization
Hyaluronic acid	Connective tissue, nerve growth factor stabilization
<i>De novo synthesized</i>	
Cytokines	
Interleukins (IL)-1,2,3,4,5,6,9,10,13,16	Inflammation, leukocyte migration, pain
INF- γ ; MIF; TNF- α	Inflammation, leukocyte proliferation/activation
Growth factors	
CSF, GM-CSF, b-FGF, NGF, VEGF	Growth of a variety of cells
Phospholipid metabolites	
Leukotriene B ₄ (LTB ₄)	Leukocyte chemotaxis
Leukotriene C ₄ (LTC ₄)	Vasoconstriction, pain
Platelet-activating factor (PAF)	Platelet activation, vasodilation
Prostaglandin D ₂ (PGD ₂)	Bronchoconstriction, pain
Nitric oxide (NO)	Vasodilation

ABBREVIATIONS: TNF- α : tumor necrosis factor- α ; INF γ : Interferon- γ ; MIF: macrophage inflammatory factor; GM-CSF: granulocyte monocyte-colony stimulating factor; b-FGF: fibroblast growth factor; NGF: nerve growth factor; SCF: stem cell factor; VEGF: vascular endothelial growth factor.

TABLE 2. Mast cell triggers

Antigen + IgE
Anaphylatoxins
CRH
IL-1
Immunoglobulin-free light chains
LPS
NGF
NT
SCF
SP
Superantigens
Ucn
VIP
Viral DNA sequences

ABBREVIATIONS: CRH: corticotropin-releasing hormone; IL: interleukin; LPS: lipopolysaccharide; NGF: nerve growth factor; NT: neurotensin; SCF: stem cell factor; SP: substance P; Ucn: urocortin; VIP: vasoactive intestinal peptide.

are present in the skin.⁵⁵ Acute stress releases CRH in the skin,⁵⁶ inducing a local response.⁵⁴ Acute stress also induces redistribution of leukocytes from the systemic circulation to the skin⁵⁷; it also exacerbates skin delayed hypersensitivity reactions⁵⁸ and chronic contact dermatitis in rats, an effect that depends on mast cells and CRH-1 receptors (CRHR-1).⁵⁹

Computer-induced stress enhanced allergen-specific responses with concomitant increase in plasma SP levels in patients with atopic dermatitis.⁶⁰ Similar findings with increased plasma levels of SP, VIP, and NGF, along with a switch to a TH2 cytokine pattern, were reported in patients with atopic dermatitis playing video games.⁶¹ Exercise was also shown to increase the

TABLE 3. Inflammatory diseases involving mast cells

Disease	Pathophysiologic effects
Asthma	Bronchostriction, pulmonary inflammation
Atopic dermatitis	Skin vasodilation, T-cell recruitment, inflammation, itching
Coronary artery disease	Coronary inflammation, myocardial ischemia
Chronic prostatitis	Prostate inflammation
Chronic rhinitis	Nasal inflammation
Fibromyalgia	Muscle inflammation, pain
Interstitial cystitis	Bladder mucosal damage, inflammation, pain
Migraine	Meningeal vasodilation, inflammation, pain
Multiple sclerosis	Increased blood-brain barrier permeability, brain inflammation, Demyelination
Neurofibromatosis	Skin nerve growth, fibrosis
Osteoarthritis	Articular erosion, inflammation, pain
Rheumatoid arthritis	Joint inflammation, cartilage erosion

TABLE 4. Selective release of mast cell mediators

Stimuli	MC type	Mediators released	Mediators not released	Physiological importance	References
Endogenous					
IL-1 β	RPMC	NO	PAF, H	Inflammation	194
PGE ₂	RPMC	IL-6	H, TNF- α	Cytoprotection	195
SCF	BMMC	IL-6	H, LTC ₄ , TNF- α	MC development	33
IL-12	RPMC	INF- γ	H	Th1 immunity	196
CD8 ligands	RPMC	TNF- α , NO	H	T cell interaction	197
Thrombin	BMMC	IL-6	5HT, TNF- α	Anticlotting	198
SCF	hCBMC	IL-8	H, GM-CSF, INF- γ , IL-1 β	Endothelial transmigration	199
Monomeric IgE	BMMC	IL-6	H, LTC ₄	MC survival	200
Endothelin-1-3	RMMC	TNF- α , IL-12 \uparrow	IL-4, IL-10, IL-13 \downarrow *	Th1 immunity	201
LTC ₄ /LTD ₄	IL-4-primed hCBMC	TNF- α , MIP-1 α , IL-5	H	Non-IgE mediated inflammation	202
IL-1	hCBMC	IL-6, IL-8, TNF	H, tryptase	Inflammation	35
CRHR-1	hCBMC	VEGF	H, tryptase, IL-8	Inflammation	77
CRHR-2	hCBMC	IL-6	H, tryptase, IL-8, VEGF	Inflammation	203
Exogenous/ Pharmacological					
Amisriptyline	RPMC	Serotonin	H	Headaches	18
LPS	RPMC	IL-6	H	Bacterial infection	31
CpG DNA	BMMC	TNF- α , IL-6	HA, IL-4, IL-12, GM-CSF, INF- γ	Host response to bacteria	204
Cholera Toxin	RPMC	IL-6	H, TNF- α	Inflammation	205
PMA	BMMC	VPF/VEGF	5HT	Angiogenesis	4
<i>Clostridium difficile</i> toxin A	RPMC	TNF- α	H	GI tract inflammation	206
<i>H. pylori</i> VacA toxin	BMMC	IL-6, IL-8, TNF- α	H	Gastric injury	150
Suboptimal Fc ϵ RI stimulation	BMMC	MCP-1	IL-10, H	Chemokines \gg cytokines /H	207
<i>S.a.</i> peptidoglycan or zymosan	hCBMC	GM-CSF, IL-1 β , RANTES, LTC ₄ IL-6	β -hexosaminidase, IL-6	Exacerbation of asthma by bacterial infection	141

ABBREVIATIONS: BMMC: bone marrow mast cells; CRHR: corticotropin-releasing hormone; H: histamine; hCBMC: human cord blood mast cells; LPS: lipopolysaccharide; LTC₄: leukotriene C₄; PMA: phorbol myristate acetate; TNF- α : tumor necrosis factor- α ; NO: nitric oxide; MIP: macrophage inhibitory protein; GM-CSF: granulocyte monocyte-colony stimulating factor; 5HT: 5-hydroxytryptamine; INF- γ : interferon- γ ; MCP-1: monocyte chemoattractant protein-1; RMMC: rat mucosal mast cells; RPMC: rat peritoneal mast cells; VPF: vascular proliferating factor; MC: mast cells; IgE: immunoglobulin E; SCF: stem cell factor; GI: gastrointestinal.

responsiveness of skin mast cells to morphine only in patients with exercise-induced asthma.⁶²

CRH⁶³ and its structurally related peptide, urocortin (Ucn),⁶⁴ can activate skin mast cells and induce mast-cell-dependent vascular permeability in rodents. CRH also increases vascular permeability in human skin,⁶⁵ a process dependent on mast cells. CRH-R2 receptor expression was shown to be up-regulated in stress-induced alopecia in humans,⁶⁶ CRH-R2 expression was increased in chronic urticaria.⁶⁷ Acute restraint stress induces rat skin vascular permeability,⁶⁸ an effect inhibited by a CRH receptor antagonist and absent in mast-cell-deficient mice.^{63,64}

Proteases released from mast cells could act on plasma albumin to generate histamine-releasing peptides,^{69,70} which would further propagate mast cell activation and inflammation. Proteases could also stimulate protease-activated receptors (PARs), inducing microleakage and widespread inflammation.^{71,72} Many dermatoses, such as atopic dermatitis (AD), chronic urticaria, and psoriasis, are triggered or exacerbated by stress,⁷³ which also worsens eczema⁷⁴ and acne vulgaris.⁷⁵

Mast cells are localized close to CRH-positive neurons in the median eminence⁷⁶ and express functional CRH receptors.⁷⁷ The median eminence is rich in mast cells^{78,79} and contains most of the histamine in the brain.⁸⁰ Hypothalamic mast cell activation can stimulate the HPA axis.^{81–83} Histamine is considered a major regulator of hypothalamus⁸⁴ and can increase CRH mRNA expression there.⁸⁵ Moreover, human mast cells can synthesize and secrete large amounts of CRH⁸⁶ as well as IL-1 and IL-6, which are independent activators of the HPA axis.⁸⁷ The immunoendocrine responses to stress in chronic skin inflammatory diseases have been reviewed,^{12,88} and it was proposed that mast cells constitute the “sensor” of a “brain–skin” connection.⁸⁹

INFLAMMATORY ARTHRITIS

The presence of mast cells in joints has been known for many years.^{17,90–96} Moreover, fluid aspirated from joints of patients with arthrosynovitis contains RANTES and MCP-1,⁹⁷ both of which are potent mast cell chemoattractants.⁹ Mast cells are required for autoimmune arthritis⁹⁸ and inflammatory arthritis,⁹⁹ as knee involvement was absent in the joints of W/W^v mast cell-deficient mice as compared to their +/+ controls. Inflammatory arthritis was also significantly reduced in CRH knockout mice⁹⁹ and in mice treated with the CRH receptor-1 antagonist, Antalarmin.¹⁰⁰

Mast cells in the joints of rheumatoid arthritis (RA) patients express CRH receptors.¹⁰¹ Moreover, CRH,^{101,102} Ucn,^{103,104} and CRH receptors are increased in the joints of inflammatory and RA patients, the symptoms of whom worsen by stress.^{105,106}

ASTHMA

Asthma is one of the most common chronic illnesses, affecting roughly 300 million people worldwide.^{107,108} The morbidity and mortality due to asthma continues to increase despite advances in both our scientific knowledge, as well as in hygiene and drugs for this disease.¹⁰⁸ The World Health Organization has estimated that 1 of 250 deaths worldwide is due to asthma. These facts highlight the need for an improved understanding of the cellular and molecular mechanisms that contribute to the pathogenesis of asthma.

Recent reports indicate that stress can exacerbate asthma.^{109–114} One study indicated that maternal stress may be responsible for the subsequent cellular response in childhood asthma.¹¹⁵ It has been postulated that stress associated with urban living may contribute to poor asthma control.¹¹⁶ Stress has long been postulated to have a negative impact on asthma, but the mechanisms by which this occurs remain poorly defined.^{109,111,112,114,117,118} One study showed that adolescents with asthma in a low socioeconomic group, who reported more stressful and acute life events, had more asthma exacerbation and higher serum Th-2 cytokines than those in higher socioeconomic status.¹¹⁹ The Inner City Asthma Study showed a correlation between community violence and asthma morbidity.¹²⁰ Post-traumatic psychological stress following the 9/11 attacks on the World Trade Center correlated with increased symptom severity in subjects with moderate-to-severe asthma and with utilization of urgent care in New York City.^{121,122} In an epidemiological study carried out among 10,667 Finnish first-year university students (18–25 years old), it was shown that an excess of stressful events, such as concomitant severe disease or death of immediate family members or family conflicts, were associated with exacerbation of asthma.¹¹¹

Stress associated with final examinations, as compared to mid semester, of college students with mild asthma increased sputum eosinophil counts, as well as eosinophil-derived neurotoxin and IL-5 once the eosinophils were cultured for up to 24 h.¹¹⁷ It was suggested that a shift in cytokine generation to that of a Th2 type may be the defining parameter.¹¹³ In one longitudinal study of 92 adults with asthma, it was determined that subjects who reported more negative life events and had low levels of social support had more episodes of asthma exacerbation induced by upper respiratory tract infections.¹²³ A large prospective long-term follow-up community-based cohort study of young adults showed a dose–response relationship between panic and asthma.¹²⁴ In fact, one study indicated that maternal stress may be responsible for the cellular response in childhood asthma,¹¹⁵ while another showed that greater levels of caregiver-perceived stress at 2–3 months was associated with increased risk of subsequent repeated wheezing among children during the first 14 months of life.¹²⁵ Such findings cannot be easily explained as the HPA axis apparently functions normally in asthmatic adult patients, producing appropriate plasma cortisol

increases in response to stress¹²⁶ which might be expected to reduce rather than exacerbate asthma symptoms. One publication showed a significantly blunted cortisol response to stress only in asthmatic children,¹²⁷ suggesting there may be differences due to age.

While no animal model exactly replicates human asthma, the use of animals has provided helpful information about the mechanisms of airway inflammation and hyperreactivity seen in asthma.^{128,129} Chronic exposure to aerosolized ovalbumin has been shown to be a useful murine model of asthma leading to airway inflammation, airway hyperresponsiveness (AHR),¹³⁰ as well as microvascular leakage in the airways.¹³⁰⁻¹³² Microvascular leakage in the airway wall may also be important for the airway wall remodeling that is found in most asthmatics.^{133,134} More recently, the house dust mite allergen model has been shown to effectively induce chronic airway inflammation and AHR.^{133,135} Stress has been shown to increase AHR¹¹⁴ and inflammation^{114,136} in response to ovalbumin challenge in murine models of asthma. In one case, exposure to an ultrasonic stressor, coinciding with the first aerosol challenge, significantly increased allergen-induced pulmonary reactivity and bronchial inflammation. Short-term (3 days) stress before allergen challenge decreased the number of inflammatory cells, but increased IL-6, while long-term (7 days) stress evidently increased the number of inflammatory cells but did not alter IL-6 levels.¹³⁶

The role of mast cells in asthma is undisputed.¹³⁷⁻¹³⁹ Rodent mast cells express bacterial Toll-like receptors (TLRs) 2 and 4.^{140,141} However, the pattern of response may be species- and tissue-specific, making generalizations difficult. TLRs were initially discovered in *Drosophila* as the receptors responsible for dorso-ventral patterning in the developing embryo; however, soon after they were shown to be important in the development of innate immunity to invading pathogens.¹⁴² Subsequently, human homologues for TLRs were identified beginning with TLR-4, which was shown to bind lipopolysaccharide (LPS). Ten human TLRs have been identified so far.¹⁴³⁻¹⁴⁵ Evidence is building that TLRs play an important role in recognition of ligands associated with bacterial or viral infections, and play a key role in the development of adaptive immune responses,¹⁴⁴ especially in asthma.¹⁴⁶ LPS induced release of TNF- α through TLR-4, while peptidoglycan induced histamine release through TLR-2 from rodent mast cells. Fetal rat skin-derived mast cells expressed TLR-3, 7, and 9 and activation by CPG oligodeoxynucleotide induced release of TNF and IL-6, as well as RANTES and MIP, but without degranulation.^{147,148} In another paper, LPS could not induce release of GM-CSF, IL-1, or LTC₄.¹⁴¹ However, LPS did induce secretion of TH2 cytokines IL-5, IL-10, and IL-13 and increased their production by Fc ϵ RI cross-linking.¹⁴⁹ Elsewhere, it was shown that TLR-2 activation produced IL-4, IL-6, and IL-13, but not IL-1,¹⁵⁰ while LPS produced TNF, IL-1, IL-6, and IL-13, but not IL-4 or IL-5, without degranulation.¹⁵⁰ Activation of these receptors even in human cultured mast cells leads to distinct biological effects: Human mast cells express viral TLR-9,¹⁵¹

activation of which produced the proinflammatory cytokine IL-6,¹⁵¹ while they produced IFN in response to double-stranded RNA through TLR-3.¹⁵² These findings may explain how viral infections worsen asthma.

Viral infections have been shown to exacerbate asthma and contribute to as many as 50% of asthma-associated deaths; moreover, more than 80% of childhood asthma exacerbations are associated with viral airway infections.¹⁵³ A number of studies have shown that viral infections increase airway hyperresponsiveness and antigen sensitization,¹⁵⁴ as well as recruitment of inflammatory cells.¹⁵⁵ Synoptical virus, metapneumovirus, rhinovirus, adenovirus,¹⁵⁶ as well as influenza and parainfluenza virus have been implicated in the pathogenesis of asthma.¹⁵⁷⁻¹⁵⁹ In fact, rhinovirus infections during infancy appear to predict childhood wheezing,¹⁶⁰ while respiratory syncytial virus during the first 3 months of life was shown to promote a TH2 response, especially significantly high levels of IL-4.¹⁶¹ Such early-infancy viral respiratory infections may also induce metalloproteinases, which are involved in airway remodeling in asthma.¹⁶² However, this field is quite confusing because current discussions focus on viral nucleic acid inoculation.¹⁶³

CORONARY INFLAMMATION

Increasing evidence implicates acute psychological stress and cardiac mast cells in coronary artery disease (CAD), especially when it occurs without angina, which appears to involve a sizable portion of myocardial infarctions (MI).¹⁶⁴⁻¹⁶⁷ Cardiac mast cells can participate in the development of atherosclerosis, coronary inflammation, and cardiac ischemia.¹⁶⁸ Mast cells are particularly prominent in coronary arteries during spasm¹⁶⁹ and accumulate in the shoulder region of human coronary plaque rupture.¹⁷⁰⁻¹⁷² The human mast cell proteolytic enzyme chymase is the main cardiac source of converting enzyme that generates the coronary constrictor angiotensin II;¹⁷³ the chymase can also induce the removal of cholesterol from HDL particles and uptake by macrophages that become “foam” cells, major components of coronary atheromas.¹⁷⁴⁻¹⁷⁷ Cardiac mast-cell-derived histamine¹⁷⁸ can constrict the coronary arteries¹⁷⁹ and can sensitize nerve endings;¹⁸⁰ this is particularly important because mast cells are localized close to nerve endings in atherosclerotic coronary arteries.¹⁸¹

Acute stress induces rat cardiac mast cell activation, an effect blocked by the “mast cell stabilizer” disodium cromoglycate (cromolyn).¹⁸² Acute stress can also induce histamine release from mouse heart,¹⁸³ as well as increase serum histamine and IL-6.^{183,184} These effects are dependent on mast cells and are greater in apolipoprotein E (ApoE) knockout mice that develop atherosclerosis.^{183,184} Serum IL-6 elevations in patients with acute CAD were documented to derive primarily from the coronary sinus.¹⁸⁵ Both histamine¹⁸⁶ and

IL-6¹⁸⁷ are significant independent factors of CAD morbidity and mortality. There are also reports of anaphylactic CAD that has been termed the “Kounis” syndrome.^{188,189}

CONCLUSION

Mast cells have emerged as unique immune cells that can be activated by many immune and nonimmune triggers, including acute stress through CRH; it is, therefore, proposed that CRH be renamed SRH (**Stress Response Hormone**) to reflect its versatile role in stress. Mast cells are critical in the development of inflammatory diseases, especially dermatoses, asthma, arthritis, and CAD. Inhibition of mast cell activation by CRH,¹⁹⁰ therefore, is a novel target for the development of new treatments for inflammatory and autoimmune disorders. Certain dietary supplements have recently been shown to be effective in this regard¹⁹¹ because they combine the proteoglycan chondroitin sulfate¹⁹² and the flavonoid quercetin,¹⁹³ both of which have mast cell inhibitory and anti-inflammatory actions.

ACKNOWLEDGMENTS

Aspects of the work discussed were supported in part by NIH Grant No. AR47652, and by a grant from Theta Biomedical Consulting and Development Co., Inc. (Brookline, MA) to T.C.T. who has been awarded U.S. patents #5250529; #6020305; #5648350; #5855884; #5821259; #5994357; #6624148 and #6984667 covering the use of CRH and mast cell blockers in the diseases described above. We thank Ms. Jessica Christian for her patience and word processing skills.

REFERENCES

1. BLANK, U. & J. RIVERA. 2004. The ins and outs of IgE-dependent mast-cell exocytosis. *Trends Immunol.* **25**: 266–273.
2. KRAFT, S., S. RANA, M.H. JOUVIN, *et al.* 2004. The role of the FcεRI beta-chain in allergic diseases. *Int. Arch. Allergy Immunol.* **135**: 62–72.
3. GRUTZKAU, A., S. KRUGER-KRASAGAKES, H. BAUMEISTER, *et al.* 1998. Synthesis, storage and release of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) by human mast cells: implications for the biological significance of VEGF₂₀₆. *Mol. Biol. Cell* **9**: 875–884.
4. BOESIGER, J., M. TSAI, M. MAURER, *et al.* 1998. Mast cells can secrete vascular permeability factor/vascular endothelial cell growth factor and exhibit enhanced release after immunoglobulin E-dependent upregulation of Fcε receptor I expression. *J. Exp. Med.* **188**: 1135–1145.

5. GALLI, S.J., S. NAKAE & M. TSAI. 2005. Mast cells in the development of adaptive immune responses. *Nat. Immunol.* **6**: 135–142.
6. RODEWALD, H.R., M. DESSING, A.M. DVORAK, *et al.* 1996. Identification of a committed precursor for the mast cell lineage. *Science* **271**: 818–822.
7. CHEN, C.C., M.A. GRIMBALDESTON, M. TSAI, *et al.* 2005. Identification of mast cell progenitors in adult mice. *Proc. Natl. Acad. Sci. USA* **102**: 11408–11413.
8. ALOE, L. & R. LEVI-MONTALCINI. 1977. Mast cells increase in tissues of neonatal rats injected with the nerve growth factor. *Brain Res.* **133**: 358–366.
9. CONTI, P., X. PANG, W. BOUCHER, *et al.* 1997. Impact of RANTES and MCP-1 chemokines on *in vivo* basophilic mast cell recruitment in rat skin injection model and their role in modifying the protein and mRNA levels for histidine decarboxylase. *Blood* **89**: 4120–4127.
10. ROTTEM, M. & Y.A. MEKORI. 2005. Mast cells and autoimmunity. *Autoimmun. Rev.* **4**: 21–27.
11. GALLI, S.J., J. KALESNIKOFF, M.A. GRIMBALDESTON, *et al.* 2005. Mast cells as “tunable” effector and immunoregulatory cells: recent advances. *Annu. Rev. Immunol.* **23**: 749–786.
12. THEOHARIDES, T.C. & D.E. COCHRANE. 2004. Critical role of mast cells in inflammatory diseases and the effect of acute stress. *J. Neuroimmunol.* **146**: 1–12.
13. KRANEVELD, A.D., M. KOOL, A.H. VAN HOUWELINGEN, *et al.* 2005. Elicitation of allergic asthma by immunoglobulin free light chains. *Proc. Natl. Acad. Sci. USA* **102**: 1578–1583.
14. REDEGELD, F.A., M.W. VAN DER HEIJDEN, M. KOOL, *et al.* 2002. Immunoglobulin-free light chains elicit immediate hypersensitivity-like responses. *Nat. Med.* **8**: 694–701.
15. REDEGELD, F.A. & F.P. NIJKAMP. 2003. Immunoglobulin free light chains and mast cells: pivotal role in T-cell-mediated immune reactions? *Trends Immunol.* **24**: 181–185.
16. BENOIST, C. & D. MATHIS. 2002. Mast cells in autoimmune disease. *Nature* **420**: 875–878.
17. WOOLLEY, D.E. 2003. The mast cell in inflammatory arthritis. *N. Engl. J. Med.* **348**: 1709–1711.
18. THEOHARIDES, T.C., P.K. BONDY, N.D. TSAKALOS, *et al.* 1982. Differential release of serotonin and histamine from mast cells. *Nature* **297**: 229–231.
19. THEOHARIDES, T.C. & W.W. DOUGLAS. 1978. Somatostatin induces histamine secretion from rat peritoneal mast cells. *Endocrinology* **102**: 1637–1640.
20. DIMITRIADOU, V., M. LAMBRACHT-HALL, J. REICHLER, *et al.* 1990. Histochemical and ultrastructural characteristics of rat brain perivascular mast cells stimulated with compound 48/80 and carbachol. *Neuroscience* **39**: 209–224.
21. DIMITRIADOU, V., M.G. BUZZI, M.A. MOSKOWITZ, *et al.* 1991. Trigeminal sensory fiber stimulation induces morphologic changes reflecting secretion in rat dura mast cells. *Neuroscience* **44**: 97–112.
22. THEOHARIDES, T.C., G.R. SANT, M. EL-MANSOURY, *et al.* 1995. Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. *J. Urol.* **153**: 629–636.
23. LETOURNEAU, R., X. PANG, G.R. SANT, *et al.* 1996. Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. *Br. J. Urol.* **77**: 41–54.

24. DVORAK, A.M., R.S. MCLEOD, A. ONDERDONK, *et al.* 1992. Ultrastructural evidence for piecemeal and anaphylactic degranulation of human gut mucosal mast cells *in vivo*. *Int. Arch. Allergy Immunol.* **99**: 74–83.
25. KOPS, S.K., H. VAN LOVEREN, R.W. ROSENSTEIN, *et al.* 1984. Mast cell activation and vascular alterations in immediate hypersensitivity-like reactions induced by a T cell derived antigen-binding factor. *Lab. Invest.* **50**: 421–434.
26. VAN LOVEREN, H., S.K. KOPS & P.W. ASKENASE. 1984. Different mechanisms of release of vasoactive amines by mast cells occur in T cell-dependent compared to IgE-dependent cutaneous hypersensitivity responses. *Eur. J. Immunol.* **14**: 40–47.
27. KOPS, S.K., T.C. THEOHARIDES, C.T. CRONIN, *et al.* 1990. Ultrastructural characteristics of rat peritoneal mast cells undergoing differential release of serotonin without histamine and without degranulation. *Cell Tissue Res.* **262**: 415–424.
28. BENYON, R., C. ROBINSON & M.K. CHURCH. 1989. Differential release of histamine and eicosanoids from human skin mast cells activated by IgE-dependent and non-immunological stimuli. *Br. J. Pharmacol.* **97**: 898–904.
29. LEVI-SCHAFFER, F. & M. SHALIT. 1989. Differential release of histamine and prostaglandin D₂ in rat peritoneal mast cells activated with peptides. *Int. Arch. Allergy Appl. Immunol.* **90**: 352–357.
30. VAN HAASTER, C.M., W. ENGELS, P.J.M.R. LEMMENS, *et al.* 1995. Differential release of histamine and prostaglandin D₂ in rat peritoneal mast cells: roles of cytosolic calcium and protein tyrosine kinases. *Biochim. Biophys. Acta* **1265**: 79–88.
31. LEAL-BERUMEN, I., P. CONLON & J.S. MARSHALL. 1994. IL-6 production by rat peritoneal mast cells is not necessarily preceded by histamine release and can be induced by bacterial lipopolysaccharide. *J. Immunol.* **152**: 5468–5476.
32. MARQUARDT, D.L., J.L. ALONGI & L.L. WALKER. 1996. The phosphatidylinositol 3-kinase inhibitor wortmannin blocks mast cell exocytosis but not IL-6 production. *J. Immunol.* **156**: 1942–1945.
33. GAGARI, E., M. TSAI, C.S. LANTZ, *et al.* 1997. Differential release of mast cell interleukin-6 via c-kit. *Blood* **89**: 2654–2663.
34. HOJO, H., R. SUN, Y. ONO, *et al.* 1996. Differential production of interleukin-6 and its close relation to liver metastasis in clones from murine P815 mastocytoma. *Cancer Lett.* **108**: 55–59.
35. KANDERE-GRZYBOWSKA, K., R. LETOURNEAU, W. BOUCHER, *et al.* 2003. IL-1 induces vesicular secretion of IL-6 without degranulation from human mast cells. *J. Immunol.* **171**: 4830–4836.
36. CAO, J., C.L. CURTIS & T.C. THEOHARIDES. 2006. Corticotropin-releasing hormone (CRH) induces vascular endothelial growth factor (VEGF) release from human mast cells via the cAMP/protein kinase A/p38 MAPK pathway. *Mol. Pharmacol.* **69**: 998–1006.
37. LEUNG, D.Y., L.A. DIAZ, V. DELEO, *et al.* 1997. Allergic and immunologic skin disorders. *JAMA* **278**: 1914–1923.
38. CHARLESWORTH, E.N. 1995. Role of basophils and mast cells in acute and late reactions in the skin. *Chem. Immunol.* **62**: 84–107.
39. CHURCH, M.K. & G.F. CLOUGH. 1999. Human skin mast cells: *in vitro* and *in vivo* studies. *Ann. Allergy Asthma Immunol.* **83**: 471–475.
40. NOLI, C. & A. MIOLO. 2001. The mast cell in wound healing. *Vet. Dermatol.* **12**: 303–313.

41. JARVIKALLIO, A., I.T. HARVIMA & A. NAUKKARINEN. 2003. Mast cells, nerves and neuropeptides in atopic dermatitis and nummular eczema. *Arch. Dermatol. Res.* **295**: 2–7.
42. WIESNER-MENZEL, L., B. SCHULZ, F. VAKILZADEH, *et al.* 1981. Electron microscopical evidence for a direct contact between nerve fibers and mast cells. *Acta Derm. Venereol. (Stockh)* **61**: 465–469.
43. GOETZL, E.J., T. CHERNOV, F. RENOLD, *et al.* 1985. Neuropeptide regulation of the expression of immediate hypersensitivity. *J. Immunol.* **135**: 802s–805s.
44. FOREMAN, J.C. 1987. Neuropeptides and the pathogenesis of allergy. *Allergy* **42**: 1–11.
45. CHURCH, M.K., M.A. LOWMAN, P.H. REES, *et al.* 1989. Mast cells, neuropeptides and inflammation. *Agents Actions* **27**: 8–16.
46. GOETZL, E.J., P.P.J. CHENG, A. HASSNER, *et al.* 1990. Neuropeptides, mast cells and allergy: novel mechanisms and therapeutic possibilities. *Clin. Exp. Allergy* **20**: 3–7.
47. CARRAWAY, R., D.E. COCHRANE, J.B. LANSMAN, *et al.* 1982. Neurotensin stimulates exocytotic histamine secretion from rat mast cells and elevates plasma histamine levels. *J. Physiol.* **323**: 403–414.
48. WATT, F.M. 1991. Cell culture models of differentiation. *FASEB J.* **5**: 287–294.
49. FEWTRELL, C.M.S., J.C. FOREMAN, C.C. JORDAN, *et al.* 1982. The effects of substance P on histamine and 5-hydroxytryptamine release in the rat. *J. Physiol.* **330**: 393–411.
50. ODUM, L., L.J. PETERSEN, P.S. SKOV, *et al.* 1998. Pituitary adenylate cyclase activating polypeptide (PACAP) is localized in human dermal neurons and causes histamine release from skin mast cells. *Inflamm. Res.* **47**: 488–492.
51. TOYODA, M., T. MAKINO, M. KAGOURA, *et al.* 2000. Immunolocalization of substance P in human skin mast cells. *Arch. Dermatol. Res.* **292**: 418–421.
52. XIANG, Z. & G. NILSSON. 2000. IgE receptor-mediated release of nerve growth factor by mast cells. *Clin. Exp. Allergy* **30**: 1379–1386.
53. SLOMINSKI, A. & J. WORTSMAN. 2000. Neuroendocrinology of the skin. *Endocr. Rev.* **21**: 457–487.
54. SLOMINSKI, A., J. WORTSMAN, T. LUGER, *et al.* 2000. Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress. *Physiol. Rev.* **80**: 979–1020.
55. SLOMINSKI, A., J. WORTSMAN, A. PISARCHIK, *et al.* 2001. Cutaneous expression of corticotropin-releasing hormone (CRH), urocortin, and CRH receptors. *FASEB J.* **15**: 1678–1693.
56. LYTINAS, M., D. KEMPURAJ, M. HUANG, *et al.* 2003. Acute stress results in skin corticotropin-releasing hormone secretion, mast cell activation and vascular permeability, an effect mimicked by intradermal corticotropin-releasing hormone and inhibited by histamine-1 receptor antagonists. *Int. Arch. Allergy Immunol.* **130**: 224–231.
57. DHABHAR, F. & B.S. MCEWEN. 1996. Stress-induced enhancement of antigen-specific cell-mediated immunity. *J. Immunol.* **156**: 2608–2615.
58. DHABHAR, F.S. & B.S. MCEWEN. 1999. Enhancing versus suppressive effects of stress hormones on skin immune function. *Proc. Natl. Acad. Sci. USA* **96**: 1059–1064.
59. KANEKO, K., S. KAWANA, K. ARAI, *et al.* 2003. Corticotropin-releasing factor receptor type 1 is involved in the stress-induced exacerbation of chronic contact dermatitis in rats. *Exp. Dermatol.* **12**: 47–52.

60. KIMATA, H. 2003. Enhancement of allergic skin wheal responses and *in vitro* allergen-specific IgE production by computer-induced stress in patients with atopic dermatitis. *Brain Behav. Immun.* **17**: 134–138.
61. KIMATA, H. 2003. Enhancement of allergic skin wheal responses in patients with atopic eczema/dermatitis syndrome by playing video games or by a frequently ringing mobile phone. *Eur. J Clin. Invest* **33**: 513–517.
62. CHOI, I.S., Y.I. KOH, S.W. CHUNG, *et al.* 2004. Increased releasability of skin mast cells after exercise in patients with exercise-induced asthma. *J. Korean Med. Sci.* **19**: 724–728.
63. THEOHARIDES, T.C., L.K. SINGH, W. BOUCHER, *et al.* 1998. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its pro-inflammatory effects. *Endocrinology* **139**: 403–413.
64. SINGH, L.K., W. BOUCHER, X. PANG, *et al.* 1999. Potent mast cell degranulation and vascular permeability triggered by urocortin through activation of CRH receptors. *J. Pharmacol. Exp. Ther.* **288**: 1349–1356.
65. CLIFTON, V.L., R. CROMPTON, R. SMITH, *et al.* 2002. Microvascular effects of CRH in human skin vary in relation to gender. *J. Clin. Endocrinol. Metab.* **87**: 267–270.
66. KATSAROU-KATSARI, A., L.K. SINGH & T.C. THEOHARIDES. 2001. Alopecia areata and affected skin CRH receptor upregulation induced by acute emotional stress. *Dermatology* **203**: 157–161.
67. PAPADOPOULOU, N., D. KALOGEROMITROS, N.G. STAURIANEAS, *et al.* 2005. Corticotropin-releasing hormone receptor-1 and histidine decarboxylase expression in chronic urticaria. *J. Invest. Dermatol.* **125**: 952–955.
68. SINGH, L.K., X. PANG, N. ALEXACOS, *et al.* 1999. Acute immobilization stress triggers skin mast cell degranulation via corticotropin releasing hormone, neurotensin and substance P: a link to neurogenic skin disorders. *Brain Behav. Immun.* **13**: 225–239.
69. CARRAWAY, R.E., D.E. COCHRANE, W. BOUCHER, *et al.* 1989. Structures of histamine-releasing peptides formed by the action of acid proteases on mammalian albumin(s). *J. Immunol.* **143**: 1680–1684.
70. COCHRANE, D.E., R.E. CARRAWAY, R.S. FELDBERG, *et al.* 1993. Stimulated rat mast cells generate histamine-releasing peptide from albumin. *Peptides* **14**: 117–123.
71. SCHMIDLIN, F. & N.W. BUNNETT. 2001. Protease-activated receptors: how proteases signal to cells. *Curr. Opin. Pharmacol.* **1**: 575–582.
72. MOLINO, M., E.S. BARNATHAN, R. NUMEROF, *et al.* 1997. Interactions of mast cell tryptase with thrombin receptors and PAR-2. *J. Biol. Chem.* **272**: 4043–4049.
73. KATSAROU-KATSARI, A., A. FILIPPOU & T.C. THEOHARIDES. 1999. Effect of stress and other psychological factors on the pathophysiology and treatment of dermatoses. *Int. J. Immunopathol. Pharmacol.* **12**: 7–11.
74. GRAHAM, D.T. & S. WOLF. 1953. The relation of eczema to attitude and to vascular reactions of the human skin. *J. Lab. Clin. Med.* **42**: 238–254.
75. MURPHY, P.M. 2001. Chemokines and the molecular basis of cancer metastasis. *N. Engl. J. Med.* **345**: 833–835.
76. THEOHARIDES, T.C., C.P. SPANOS, X. PANG, *et al.* 1995. Stress-induced intracranial mast cell degranulation. A corticotropin releasing hormone-mediated effect. *Endocrinology* **136**: 5745–5750.

77. CAO, J., N. PAPADOPOULOU, D. KEMPURAJ, *et al.* 2005. Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor (VEGF). *J. Immunol.* **174**: 7665–7675.
78. POLLARD, H., S. BISCHOFF, C. LLORENS-CORTES, *et al.* 1976. Histidine decarboxylase and histamine in discrete nuclei of rat hypothalamus and the evidence for mast cells in the median eminence. *Brain Res.* **118**: 509–513.
79. PANULA, P., H.-Y.T. YANG & E. COSTA. 1984. Histamine-containing neurons in the rat hypothalamus. *Proc. Natl. Acad. Sci. USA* **81**: 2572–2576.
80. YAMATODANI, A., K. MAEYAMA, T. WATANABE, *et al.* 1982. Tissue distribution of histamine in a mutant mouse deficient in mast cells: clear evidence for the presence of non-mast cell histamine. *Biochem. Pharmacol.* **31**: 305–309.
81. BUGAJSKI, A.J., Z. CHLAP, A. GADEK-MICHALSKA, *et al.* 1995. Degranulation and decrease in histamine levels of thalamic mast cells coincides with corticosterone secretion induced by compound 48/80. *Inflamm. Res.* **44**(Suppl.1): S50–S51.
82. GADEK-MICHALSKA, A., Z. CHLAP, M. TURON, *et al.* 1991. The intracerebroventricularly administered mast cells degranulator compound 48/80 increases the pituitary-adrenocortical activity in rats. *Agents Actions* **32**: 203–208.
83. MATSUMOTO, I., Y. INOUE, T. SHIMADA, *et al.* 2001. Brain mast cells act as an immune gate to the hypothalamic-pituitary-adrenal axis in dogs. *J. Exp. Med.* **194**: 71–78.
84. ROBERTS, F. & C.R. CALCUTT. 1983. Histamine and the hypothalamus. *Neuroscience* **9**: 721–739.
85. KJAER, A., P.J. LARSEN, U. KNIGGE, *et al.* 1998. Neuronal histamine and expression of corticotropin-releasing hormone, vasopressin and oxytocin in the hypothalamus: relative importance of H₁ and H₂ receptors. *Eur. J. Endocrinol.* **139**: 238–243.
86. KEMPURAJ, D., N.G. PAPADOPOULOU, M. LY TINAS, *et al.* 2004. Corticotropin-releasing hormone and its structurally related urocortin are synthesized and secreted by human mast cells. *Endocrinology* **145**: 43–480; Epub 2003 Oct. 23.
87. BETHIN, K.E., S.K. VOGT & L.J. MUGLIA. 2000. Interleukin-6 is an essential, corticotropin-releasing hormone-independent stimulator of the adrenal axis during immune system activation. *Proc. Natl. Acad. Sci. USA* **97**: 9317–9322.
88. BUSKE-KIRSCHBAUM, A. & D.H. HELLHAMMER. 2003. Endocrine and immune responses to stress in chronic inflammatory skin disorders. *Ann. N. Y. Acad. Sci.* **992**: 231–240.
89. PAUS, R., T.C. THEOHARIDES & P.C. ARCK. 2006. Neuroimmunoendocrine circuitry of the “brain-skin connection.” *Trends Immunol* **27**: 32–39.
90. CRISP, A.J., C.M. CHAMPAN, S.E. KIRKHAM, *et al.* 1984. Articular mastocytosis in rheumatoid arthritis. *Arthritis Rheum.* **27**: 845–851.
91. KOLDEWIJN, E.L., O.R. HOMMES, W.A.J.G. LEMMENS, *et al.* 1995. Relationship between lower urinary tract abnormalities and disease-related parameters in multiple sclerosis. *J. Urol.* **154**: 169–173.
92. WOOLLEY, D.E. 1995. Mast cells in the rheumatoid lesion—ringleaders or innocent bystanders. *Ann. Rheum. Dis.* **54**: 533–534.
93. TETLOW, L.C. & D.E. WOOLLEY. 1995. Distribution, activation and tryptase/chymase phenotype of mast cells in the rheumatoid lesion. *Ann. Rheum. Dis.* **54**: 549–555.

94. DE PAULIS, A., A. CICCARELLI, I. MARINÒ, *et al.* 1997. Human synovial mast cells. II. Heterogeneity of the pharmacologic effects of antiinflammatory and immunosuppressive drugs. *Arthritis Rheum.* **40**: 469–478.
95. DE PAULIS, A., I. MARINO, A. CICCARELLI, *et al.* 1996. Human synovial mast cells. I. Ultrastructural *in situ* and *in vitro* immunologic characterization. *Arthritis Rheum.* **39**: 1222–1233.
96. GOTIS-GRAHAM, I., M.D. SMITH, A. PARKER, *et al.* 1998. Synovial mast cell responses during clinical improvement in early rheumatoid arthritis. *Ann. Rheum. Dis.* **57**: 664–671.
97. CONTI, P., M. REALE, R.C. BARBACANE, *et al.* 2002. Differential production of RANTES and MCP-1 in synovial fluid from the inflamed human knee. *Immunol. Lett.* **80**: 105–111.
98. LEE, D.M., D.S. FRIEND, M.F. GURISH, *et al.* 2002. Mast cells: a cellular link between autoantibodies and inflammatory arthritis. *Science* **297**: 1689–1692.
99. MATTHEOS, S., S. CHRISTODOULOU, D. KEMPURAJ, *et al.* 2003. Mast cells and corticotropin-releasing hormone (CRH) are required for experimental inflammatory arthritis. *FASEB J.* **17**: C44.
100. WEBSTER, E.L., R.M. BARRIENTOS, C. CONTOREGGI, *et al.* 2002. Corticotropin releasing hormone (CRH) antagonist attenuates adjuvant induced arthritis: role of CRH in peripheral inflammation. *J. Rheumatol.* **29**: 1252–1261.
101. McEVOY, A.N., B. BRESNIHAN, O. FITZGERALD, *et al.* 2001. Corticotropin-releasing hormone signaling in synovial tissue from patients with early inflammatory arthritis is mediated by the type 1a corticotropin-releasing hormone receptor. *Arthritis Rheum.* **44**: 1761–1767.
102. LOWRY, P.J., R.J. WOODS & S. BAIGENT. 1996. Corticotropin releasing factor and its binding protein. *Pharmacol. Biochem. Behav.* **54**: 305–308.
103. UZUKI, M., H. SASANO, Y. MURAMATSU, *et al.* 2001. Urocortin in the synovial tissue of patients with rheumatoid arthritis. *Clin. Sci.* **100**: 577–589.
104. KOHNO, M., Y. KAWAHITO, Y. TSUBOUCHI, *et al.* 2001. Urocortin expression in synovium of patients with rheumatoid arthritis and osteoarthritis: relation to inflammatory activity. *J. Clin. Endocrinol. Metab.* **86**: 4344–4352.
105. THOMASON, B.T., P.J. BRANTLEY, G.N. JONES, *et al.* 1992. The relation between stress and disease activity in rheumatoid arthritis. *J. Behav. Med.* **15**: 215–220.
106. HERRMANN, M., J. SCHOLMERICH & R.H. STRAUB. 2000. Stress and rheumatic diseases. *Rheum. Dis. Clin. North Am.* **26**: 737–763.
107. WEISS, S.T. 2001. Epidemiology and heterogeneity of asthma. *Ann. Allergy Asthma Immunol.* **87**: 5–8.
108. PAPIRIS, S., A. KOTANIDOU, K. MALAGARI, *et al.* 2002. Clinical review: severe asthma. *Crit. Care* **6**: 30–44.
109. LAUBE, B.L., B.A. CURBOW & R.W. COSTELLO. 2002. A pilot study examining the relationship between stress and serum cortisol concentrations in women with asthma. *Respir. Med.* **96**: 823–828.
110. SCHMALING, K.B., P.E. MCKNIGHT & N. AFARI. 2002. A prospective study of the relationship of mood and stress to pulmonary function among patients with asthma. *J. Asthma* **39**: 501–510.
111. KILPELAINEN, M., M. KOSKENVUO, H. HELENIUS, *et al.* 2002. Stressful life events promote the manifestation of asthma and atopic diseases. *Clin. Exp. Allergy* **32**: 256–263.
112. LAWRENCE, D.A. 2002. Psychologic stress and asthma: neuropeptide involvement. *Environ. Health Perspect.* **110**: A230–A231.

113. BIENENSTOCK, J. 2002. Stress and asthma: the plot thickens. *Am. J. Respir. Crit. Care Med.* **165**: 1034–1035.
114. JOACHIM, R.A., D. QUARCOO, P.C. ARCK, *et al.* 2003. Stress enhances airway reactivity and airway inflammation in an animal model of allergic bronchial asthma. *Psychosom. Med.* **65**: 811–815.
115. VON HERTZEN, L.C. 2002. Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy. *J. Allergy Clin. Immunol.* **109**: 923–928.
116. DENDORFER, U., P. OETTGEN & T.A. LIBERMANN. 1994. Multiple regulatory elements in the interleukin-6 gene mediate induction by prostaglandins, cyclic AMP, and lipopolysaccharide. *Mol. Cell Biol.* **14**: 4443–4454.
117. LIU, L.Y., C.L. COE, C.A. SWENSON, *et al.* 2002. School examinations enhance airway inflammation to antigen challenge. *Am. J. Respir. Crit. Care Med.* **165**: 1062–1067.
118. GORDON, D.J. & B.M. RIFKIND. 1989. High-density lipoprotein—the clinical implications of recent studies. *N. Engl. J. Med.* **321**: 1311–1316.
119. CHEN, E., E.B. FISHER, L.B. BACHARIER, *et al.* 2003. Socioeconomic status, stress, and immune markers in adolescents with asthma. *Psychosom. Med.* **65**: 984–992.
120. WRIGHT, R.J., H. MITCHELL, C.M. VISNESS, *et al.* 2004. Community violence and asthma morbidity: the Inner-City Asthma Study. *Am. J. Public Health* **94**: 625–632.
121. FAGAN, J., S. GALEA, J. AHERN, *et al.* 2003. Relationship of self-reported asthma severity and urgent health care utilization to psychological sequelae of the September 11, 2001 terrorist attacks on the World Trade Center among New York City area residents. *Psychosom. Med.* **65**: 993–996.
122. CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC). 2002. Self-reported increase in asthma severity after the September 11 attacks on the World Trade Center—Manhattan, New York, 2001 *MMWR* **51**: 781–784.
123. SMITH, A. & K. NICHOLSON. 2001. Psychosocial factors, respiratory viruses and exacerbation of asthma. *Psychoneuroendocrinology* **26**: 411–420.
124. HASLER, G., P.J. GERGEN, D.G. KLEINBAUM, *et al.* 2005. Asthma and panic in young adults: a 20-year prospective community study. *Am. J. Respir. Crit. Care Med.* **171**: 1224–1230.
125. WRIGHT, R.J., S. COHEN, V. CAREY, *et al.* 2002. Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. *Am. J. Respir. Crit. Care Med.* **165**: 358–365.
126. KAPOOR, U., G. TAYAL, S.K. MITTAL, *et al.* 2003. Plasma cortisol levels in acute asthma. *Indian J. Pediatr.* **70**: 965–968.
127. BUSKE-KIRSCHBAUM, A., K. VON AUER, S. KRIEGER, *et al.* 2003. Blunted cortisol responses to psychosocial stress in asthmatic children: a general feature of atopic disease? *Psychosom. Med.* **65**: 806–810.
128. KIPS, J.C., G.P. ANDERSON, J.J. FREDBERG, *et al.* 2003. Murine models of asthma. *Eur. Respir. J.* **22**: 374–382.
129. LLOYD, C.M. & J.C. GUTIERREZ-RAMOS. 2004. Animal models to study chemokine receptor function: *in vivo* mouse models of allergic airway inflammation. *Methods Mol. Biol.* **239**: 199–210.
130. WILSON, J. 2000. The bronchial microcirculation in asthma. *Clin. Exp. Allergy* **30**: 51–53.

131. OLIVENSTEIN, R., T. DU, L.J. XU, *et al.* 1997. Microvascular leakage in the airway wall and lumen during allergen induced early and late responses in rats. *Pulm. Pharmacol. Ther.* **10**: 223–230.
132. VAN RENSEN, E.L., P.S. HIEMSTRA, K.F. RABE, *et al.* 2002. Assessment of microvascular leakage via sputum induction: the role of substance P and neurokinin A in patients with asthma. *Am. J. Respir. Crit. Care Med.* **165**: 1275–1279.
133. JOHNSON, J.R., R.E. WILEY, R. FATTOUH, *et al.* 2004. Continuous exposure to house dust mite elicits chronic airway inflammation and structural remodeling. *Am. J. Respir. Crit. Care Med.* **169**: 378–385.
134. NAURECKAS, E.T., I.M. NDUKWU, A.J. HALAYKO, *et al.* 1999. Bronchoalveolar lavage fluid from asthmatic subjects is mitogenic for human airway smooth muscle. *Am. J. Respir. Crit. Care Med.* **160**: 2062–2066.
135. SADAKANE, K., T. ICHINOSE, H. TAKANO, *et al.* 2002. Murine strain differences in airway inflammation induced by diesel exhaust particles and house dust mite allergen. *Int. Arch. Allergy Immunol.* **128**: 220–228.
136. FORSYTHE, P., C. EBELING, J.R. GORDON, *et al.* 2004. Opposing effects of short- and long-term stress on airway inflammation. *Am. J. Respir. Crit. Care Med.* **169**: 220–226.
137. CHO, S.H., A.J. ANDERSON & C.K. OH. 2002. Importance of mast cells in the pathophysiology of asthma. *Clin. Rev. Allergy Immunol.* **22**: 161–174.
138. BRADDING, P. 2003. The role of the mast cell in asthma: a reassessment. *Curr. Opin. Allergy Clin. Immunol.* **3**: 45–50.
139. BRIGHTLING, C.E., P. BRADDING, I.D. PAVORD, *et al.* 2003. New insights into the role of the mast cell in asthma. *Clin. Exp. Allergy* **33**: 550–556.
140. VARADARADJALOU, S., F. FEGER, N. THIEBLEMONT, *et al.* 2003. Toll-like receptor 2 (TLR2) and TLR4 differentially activate human mast cells. *Eur. J. Immunol.* **33**: 899–906.
141. MCCURDY, J.D., T.J. OLYNYCH, L.H. MAHER, *et al.* 2003. Cutting edge: distinct Toll-like receptor 2 activators selectively induce different classes of mediator production from human mast cells. *J. Immunol.* **170**: 1625–1629.
142. ROCK, F.L., G. HARDIMAN, J.C. TIMANS, *et al.* 1998. A family of human receptors structurally related to *Drosophila* Toll. *Proc. Natl. Acad. Sci. USA* **95**: 588–593.
143. AKIRA, S., K. TAKEDA & T. KAISHO. 2001. Toll-like receptors: critical proteins linking innate and acquired immunity. *Nat. Immunol.* **2**: 675–680.
144. ADEREM, A. & R.J. ULEVITCH. 2000. Toll-like receptors in the induction of the innate immune response. *Nature* **406**: 782–787.
145. HEINE, H. & E. LIEN. 2003. Toll-like receptors and their function in innate and adaptive immunity. *Int. Arch. Allergy Immunol.* **130**: 180–192.
146. CRISTOFARO, P. & S.M. OPAL. 2006. Role of toll-like receptors in infection and immunity: clinical implications. *Drugs* **66**: 15–29.
147. ANTHONY, M. & J.W. LANCE. 1971. Whole blood histamine and plasma serotonin in cluster headache. *Proc. Aust. Assoc. Neurol.* **8**: 43–46.
148. CAIRNS, J.A. & A.F. WALLS. 1996. Mast cell tryptase is a mitogen for epithelial cells. Stimulation of IL-8 production and intercellular adhesion molecule-1 expression. *J. Immunol.* **156**: 275–283.
149. MASUDA, A., Y. YOSHIKAI, K. AIBA, *et al.* 2002. Th2 cytokine production from mast cells is directly induced by lipopolysaccharide and distinctly regulated by c-Jun N-terminal kinase and p38 pathways. *J. Immunol.* **169**: 3801–3810.

150. SUPAJATURA, V., H. USHIO, A. NAKAO, *et al.* 2002. Differential responses of mast cell Toll-like receptors 2 and 4 in allergy and innate immunity. *J. Clin. Invest.* **109**: 1351–1359.
151. IKEDA, R.K., M. MILLER, J. NAYAR, *et al.* 2003. Accumulation of peribronchial mast cells in a mouse model of ovalbumin allergen induced chronic airway inflammation: modulation by immunostimulatory DNA sequences. *J. Immunol.* **171**: 4860–4867.
152. KULKA, M., L. ALEXOPOULOU, R.A. FLAVELL, *et al.* 2004. Activation of mast cells by double-stranded RNA: evidence for activation through Toll-like receptor 3. *J. Allergy Clin. Immunol.* **114**: 174–182.
153. O’SULLIVAN, S.M. 2005. Asthma death, CD8+ T cells, and viruses. *Proc. Am. Thorac. Soc.* **2**: 162–165.
154. DAKHAMA, A., Y.M. LEE & E.W. GELFAND. 2005. Virus-induced airway dysfunction: pathogenesis and biomechanisms. *Pediatr. Infect. Dis. J.* **24**: S159–S169, discussion.
155. VAN RIJT, L.S., C.H. VAN KESSEL, I. BOOGAARD, *et al.* 2005. Respiratory viral infections and asthma pathogenesis: a critical role for dendritic cells? *J. Clin. Virol.* **34**: 161–169.
156. SACKESSEN, C., A. PINAR, B.E. SEKEREL, *et al.* 2005. Use of polymerase chain reaction for detection of adenovirus in children with or without wheezing Turk. *J. Pediatr.* **47**: 227–231.
157. PELAIA, G., A. VATRELLA, L. GALLELLI, *et al.* 2006. Respiratory infections and asthma. *Respir. Med.* **100**: 775–784.
158. MATSUSE, H., Y. KONDO, S. SAEKI, *et al.* 2005. Naturally occurring parainfluenza virus 3 infection in adults induces mild exacerbation of asthma associated with increased sputum concentrations of cysteinyl leukotrienes. *Int. Arch. Allergy Immunol.* **138**: 267–272.
159. WILLIAMS, J.V., J.E. CROWE JR., R. ENRIQUEZ, *et al.* 2005. Human metapneumovirus infection plays an etiologic role in acute asthma exacerbations requiring hospitalization in adults. *J. Infect. Dis.* **192**: 1149–1153.
160. LEMANSKE, R.F. JR., D.J. JACKSON, R.E. GANGNON, *et al.* 2005. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J. Allergy Clin. Immunol.* **116**: 571–577.
161. KRISTJANSSON, S., S.P. BJARNARSON, G. WENNERGREN, *et al.* 2005. Respiratory syncytial virus and other respiratory viruses during the first 3 months of life promote a local TH2-like response. *J. Allergy Clin. Immunol.* **116**: 805–811.
162. GUALANO, R.C., R. VLAHOS & G.P. ANDERSON. 2006. What is the contribution of respiratory viruses and lung proteases to airway remodelling in asthma and chronic obstructive pulmonary disease? *Pulm. Pharmacol. Ther.* **19**: 18–23.
163. EDWARDS, M.R., T. KEBADZE, M.W. JOHNSON, *et al.* 2006. New treatment regimes for virus-induced exacerbations of asthma. *Pulm. Pharmacol. Ther.* **19**: 320–334.
164. DEEDWANIA, P.C. 1995. Mental stress, pain perception and risk of silent ischemia. *J. Am. Coll. Cardiol.* **25**: 1504–1506.
165. FREEMAN, L.J., P.G.F. NIXON, P. SALLABANK, *et al.* 1987. Psychological stress and silent myocardial ischemia. *Am. Heart J.* **114**: 477–482.
166. DEANFIELD, J.E., M. SHEA, M. KENSETT, *et al.* 1984. Silent myocardial ischaemia due to mental stress. *Lancet* **2**: 1001–1005.

167. ROZANSKI, A., C.N. BAIREY, D.S. KRANTZ, *et al.* 1988. Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. *N. Engl. J. Med.* **318**: 1005–1012.
168. PATELLA, V., G. DE CRESCENZO, A. CICCARELLI, *et al.* 1995. Human heart mast cells: a definitive case of mast cell heterogeneity. *Int. Arch. Allergy Immunol.* **106**: 386–393.
169. FORMAN, M.B., J.A. OATES, D. ROBERTSON, *et al.* 1985. Increased adventitial mast cells in a patient with coronary spasm. *N. Engl. J. Med.* **313**: 1138–1141.
170. KAARTINEN, M., A. PENTTILÄ & P.T. KOVANEN. 1994. Accumulation of activated mast cells in the shoulder region of human coronary atheroma, the predilection site of atheromatous rupture. *Circulation* **90**: 1669–1678.
171. CONSTANTINIDES, P. 1995. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* **92**: 1083–1088.
172. LAINE, P., M. KAARTINEN, A. PENTTILÄ, *et al.* 1999. Association between myocardial infarction and the mast cells in the adventitia of the infarct-related coronary artery. *Circulation* **99**: 361–369.
173. JENNE, D.E. & J. TSCHOPP. 1991. Angiotensin II-forming heart chymase is a mast-cell-specific enzyme. *Biochem. J.* **276**: 567.
174. LEE, M., P.T. KOVANEN, G. TEDESCHI, *et al.* 2003. Apolipoprotein composition and particle size affect HDL degradation by chymase: effect on cellular cholesterol efflux. *J. Lipid Res.* **44**: 539–546.
175. LEE, M., L. CALABRESI, G. CHIESA, *et al.* 2002. Mast cell chymase degrades apoE and apoA-II in apoA-I-knockout mouse plasma and reduces its ability to promote cellular cholesterol efflux. *Arterioscler. Thromb. Vasc. Biol.* **22**: 1475–1481.
176. KOVANEN, P.T. 1996. Mast cells in human fatty streaks and atheromas: implications for intimal lipid accumulation. *Curr. Opin. Lipidol.* **7**: 281–286.
177. LINDSTEDT, L., M. LEE, G.R. CASTRO, *et al.* 1996. Chymase in exocytosed rat mast cell granules effectively proteolyzes apolipoprotein AI-containing lipoproteins, so reducing the cholesterol efflux-inducing ability of serum and aortic intimal fluid. *J. Clin. Invest.* **97**: 2174–2182.
178. GRISTWOOD, R.W., J.C. LINCOLN, D.A. OWEN, *et al.* 1981. Histamine release from human right atrium. *Br. J. Pharmacol.* **74**: 7–9.
179. GENOVESE, A. & G. SPADARO. 1997. Highlights in cardiovascular effects of histamine and H1-receptor antagonists. *Allergy* **52**: 67–78.
180. CHRISTIAN, E.P., B.J. UNDEM & D. WEINREICH. 1989. Endogenous histamine excites neurones in the guinea pig superior cervical ganglion *in vitro*. *J. Physiol.* **409**: 297–312.
181. LAINE, P., A. NAUKKARINEN, L. HEIKKILA, *et al.* 2000. Adventitial mast cells connect with sensory nerve fibers in atherosclerotic coronary arteries. *Circulation* **101**: 1665–1669.
182. PANG, X., N. ALEXACOS, R. LETOURNEAU, *et al.* 1998. A neurotensin receptor antagonist inhibits acute immobilization stress-induced cardiac mast cell degranulation, a corticotropin-releasing hormone-dependent process. *J. Pharm. Exp. Ther.* **287**: 307–314.
183. HUANG, M., X. PANG, L. LETOURNEAU, *et al.* 2002. Acute stress induces cardiac mast cell activation and histamine release, effects that are increased in apolipoprotein E knockout mice. *Cardiovasc. Res.* **55**: 150–160.

184. HUANG, M., X. PANG, K. KARALIS, *et al.* 2003. Stress-induced interleukin-6 release in mice is mast cell-dependent and more pronounced in Apolipoprotein E knockout mice. *Cardiovasc. Res.* **59**: 241–249.
185. DELIARGYRIS, E.N., R.J. RAYMOND, T.C. THEOHARIDES, *et al.* 2000. Sites of interleukin-6 release in patients with acute coronary syndromes and in patients with congestive heart failure. *Am. J. Cardiol.* **86**: 913–918.
186. CLEJAN, S., S. JAPA, C. CLEMETSON, *et al.* 2002. Blood histamine is associated with coronary artery disease, cardiac events and severity of inflammation and atherosclerosis. *J. Cell Mol. Med.* **6**: 583–592.
187. SUZUKI, M., S. INABA, T. NAGAI, *et al.* 2003. Relation of C-reactive protein and interleukin-6 to culprit coronary artery plaque size in patients with acute myocardial infarction. *Am. J. Cardiol.* **91**: 331–333.
188. KOUNIS, N.G. & G.M. ZAVRAS. 1996. Allergic angina and allergic myocardial infarction. *Circulation* **94**: 1789.
189. KOUNIS, N.G., N.D. GRAPSAS & J.A. GOUDEVENOS. 1999. Unstable angina, allergic angina, and allergic myocardial infarction. *Circulation* **100**: e156.
190. THEOHARIDES, T.C., J.M. DONELAN, N. PAPADOPOULOU, *et al.* 2004. Mast cells as targets of corticotropin-releasing factor and related peptides. *Trends Pharmacol. Sci.* **25**: 563–568.
191. THEOHARIDES, T.C. 2003. Dietary supplements for arthritis and other inflammatory conditions: key role of mast cells and benefit of combining anti-inflammatory and proteoglycan products. *Eur. J. Inflamm.* **1**: 1–8.
192. THEOHARIDES, T.C., P. PATRA, W. BOUCHER, *et al.* 2000. Chondroitin sulfate inhibits connective tissue mast cells. *Br. J. Pharmacol.* **131**: 1039–1049.
193. MIDDLETON, E. JR., C. KANDASWAMI & T.C. THEOHARIDES. 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. *Pharmacol. Rev.* **52**: 673–751.
194. HOGABOAM, C.M., A.D. BEFUS & J.L. WALLACE. 1993. Modulation of rat mast cell reactivity by IL-1 beta. Divergent effects on nitric oxide and platelet-activating factor release. *J. Immunol.* **151**: 3767–3774.
195. LEAL-BERUMEN, I., P. O'BYRNE, A. GUPTA, *et al.* 1995. Prostanoid enhancement of interleukin-6 production by rat peritoneal mast cells. *J. Immunol.* **154**: 4759–4767.
196. GUPTA, A.A., I. LEAL-BERUMEN, K. CROITORU, *et al.* 1996. Rat peritoneal mast cells produce IFN- γ following IL-12 treatment but not in response to IgE-mediated activation. *J. Immunol.* **157**: 2123–2128.
197. LIN, T.J., N. HIRJI, O. NOHARA, *et al.* 1998. Mast cells express novel CD8 molecules that selectively modulate mediator secretion. *J. Immunol.* **161**: 6265–6272.
198. GORDON, J.R., X. ZHANG, K. STEVENSON, *et al.* 2000. Thrombin induces IL-6 but not TNF α secretion by mouse mast cells: threshold-level thrombin receptor and very low level Fc ϵ RI signaling synergistically enhance IL-6 secretion. *Cell Immunol.* **205**: 128–135.
199. LIN, T.J., T.B. ISSEKUTZ & J.S. MARSHALL. 2000. Human mast cells transmigrate through human umbilical vein endothelial monolayers and selectively produce IL-8 in response to stromal cell-derived factor-1 alpha. *J. Immunol.* **165**: 211–220.
200. KALESNIKOFF, J., M. HUBER, V. LAM, *et al.* 2001. Monomeric IgE stimulates signaling pathways in mast cells that lead to cytokine production and cell survival. *Immunity* 801–811.

201. COULOMBE, M., B. BATTISTINI, J. STANKOVA, *et al.* 2002. Endothelins regulate mediator production of rat tissue-cultured mucosal mast cells. Up-regulation of Th1 and inhibition of Th2 cytokines. *J. Leukoc. Biol.* **71**: 829–836.
202. MELLOR, E.A., K.F. AUSTEN & J.A. BOYCE. 2002. Cysteinyl leukotrienes and uridine diphosphate induce cytokine generation by human mast cells through an interleukin 4-regulated pathway that is inhibited by leukotriene receptor antagonists. *J. Exp. Med.* **195**: 583–592.
203. PAPADOPOULOU, N.G., L. OLESON, D. KEMPURAJ, *et al.* 2005. Regulation of corticotropin-releasing hormone receptor-2 expression in human cord blood-derived cultured mast cells. *J. Mol. Endocrinol.* **35**: R1–R8.
204. ZHU, F., K. GOMI & J.S. MARSHALL. 1998. Short-term and long-term cytokine release by mouse bone marrow mast cells and the differentiated KU-812 cell line are inhibited by brefeldin A. *J. Immunol.* **161**: 2541–2551.
205. LEAL-BERUMEN, I., D.P. SNIDER, C. BARAJAS-LOPEZ, *et al.* 1996. Cholera toxin increases IL-6 synthesis and decreases TNF- α production by rat peritoneal mast cells. *J. Immunol.* **156**: 316–321.
206. CALDERON, G.M., J. TORRES-LOPEZ, T.J. LIN, *et al.* 1998. Effects of toxin A from *Clostridium difficile* on mast cell activation and survival. *Infect. Immun.* **66**: 2755–2761.
207. GONZALEZ-ESPINOSA, C., S. ODOM, A. OLIVERA, *et al.* 2003. Preferential signaling and induction of allergy-promoting lymphokines upon weak stimulation of the high affinity IgE receptor on mast cells. *J. Exp. Med.* **197**: 1453–1465.